Cholinergic Pathways and the Ascending Reticular Activating System of the Human Brain[a]

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The primate brain contains eight major cholinergic cell groups that project to other central nervous system structures. Many of these cholinergic cell groups do not respect traditional nuclear boundaries and their constituent cells are intermixed with other noncholinergic neurons. We therefore introduced the Ch1–Ch8 nomenclature in order to designate the cholinergic (i.e., choline acetyltransferase-containing) neurons within these eight cell groups.[1]

According to this nomenclature, Ch1 designates the cholinergic cells associated with the medial septal nucleus, Ch2 those associated with the vertical nucleus of the diagonal band, Ch3 those associated with the horizontal limb of the diagonal band nucleus, Ch4 those associated with the nucleus basalis of Meynert, Ch5 those associated with the pedunculopontine nucleus of the rostral brain stem, Ch6 those associated with the laterodorsal tegmental nucleus also in the rostral brain stem, Ch7 those in the medial habenula, and Ch8 those in the parabigeminal nucleus.

Tracer experiments in a number of animal species have shown that Ch1 and Ch2 provide the major cholinergic innervation for the hippocampal complex, Ch3 for the olfactory bulb, Ch4 for the cerebral cortex and amygdala, Ch5 and Ch6 for the thalamus, Ch7 for interpeduncular nucleus, and Ch8 for the superior colliculus. There are also lesser connections from Ch1–Ch4 and Ch8 to the thalamus and from Ch5–Ch6 to the cerebral cortex.[1,2]

In the rodent brain, intrinsic cholinergic interneurons may provide up to 30% of the cholinergic innervation in the cerebral cortex. No such cholinergic interneurons have been reported in the adult primate cerebral cortex or in the thalamus of any species studied thus far. The cholinergic innervation of the adult primate cerebral cortex and thalamus is therefore almost exclusively extrinsic.

CHOLINERGIC NEURONS OF THE BASAL FOREBRAIN

The basal forebrain of the primate brain contains four overlapping constellations of cholinergic projection neurons. Studies in the monkey brain show that approximately 10% of perikarya within the boundaries of the medial septal nucleus are cholinergic and belong to the Ch1 cell group; approximately 70% of neurons in the

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vertical limbic nucleus of the diagonal band are cholinergic and belong to the Ch2 cell group; less than 5% of neurons in the horizontal nucleus of the diagonal band are cholinergic and belong to the Ch3 cell group; approximately 90% of the large neurons in the nucleus basalis of the substantia innominata are cholinergic and belong to the Ch4 cell group. Of these four cholinergic cell groups, the Ch4 group is by far the largest and the one that has been most extensively studied in the human brain.[3,4]

Because nearly 90% of the nucleus basalis (NB) neurons in the human brain express choline acetyltransferase (and therefore belong to Ch4), this cell group can also be designated as the NB-Ch4 complex. The more general term "NB" can be used to designate all of the components in this nucleus (large and small cells, cholinergic and noncholinergic), whereas the more restrictive Ch4 designation is reserved for the contingent of cholinergic NB neurons as revealed by ChAT immunohistochemistry.

The human NB-Ch4 extends from the level of the olfactory tubercle to that of the anterior hippocampus, spanning a distance of 13–14 mm in the sagittal plane. It attains its greatest mediolateral width of 18 mm within the substantia innominata (subcommissural gray). Arendt *et al.*[5] estimated that the human NB-Ch4 complex contains 200,000 neurons in each hemisphere. Thus, the NB-Ch4 contains at least 10 times as many neurons as the nucleus locus coeruleus, which has approximately 15,000 neurons in the adult human brain.[6] On topographical grounds, the constituent neurons of the human NB-Ch4 complex can be subdivided into six sectors that occupy its anteromedial (Ch4am), anterolateral (NB-Ch4al), anterointermediate (NB-Ch4ai), intermediodorsal (NB-Ch4id), intermedioventral (NB-Ch4iv), and posterior (NB-Ch4p) regions.

Gorry[7] has shown that the NB displays a progressive evolutionary trend, becoming more and more extensive and differentiated in more highly evolved species, especially in primates and cetacea. Our observations are consistent with this general view and show that the human NB-Ch4 is a highly differentiated and relatively large structure. Although many morphological features of the human NB-Ch4 are similar to those described for the rhesus monkey, there is also a sense of increased complexity and differentiation. For example, a prominent Ch4ai sector is easily identified in the human brain but not in the rhesus monkey. In addition to these "compact" neuronal sectors, the Ch4 complex also contains "interstitial" elements that are embedded within the internal capsule, the diagonal band of Broca, the anterior commissure, the ansa peduncularis, the inferior thalamic peduncle, and the ansa lenticularis (FIG. 1). The physiological implications of this intimate association with fiber bundles are unknown. Conceivably, the NB-Ch4 complex, and especially its interstitial components, could monitor and perhaps influence the physiological activity along these fiber tracts. The presence of these interstitial components outside the traditional boundaries of the nucleus basalis is another reason why Ch4 and NB are not synonymous terms.

No strict delineation exists between the boundaries of NB-Ch4 and adjacent cell groups such as those of the olfactory tubercle, preoptic area, hypothalamic nuclei, striatal structures, nuclei of the diagonal band, amygdaloid nuclei, and globus pallidus. In addition to this "open" nuclear structure, the neurons of NB-Ch4 are heteromorphic in shape and have an isodendritic morphology with overlapping dendritic fields, many of which extend into fiber tracts traversing the basal forebrain. These characteristics are also present in the nuclei of the brain-stem reticular formation and have led to the suggestion that the NB-Ch4 complex could be conceptualized as a telencephalic extension of the brain-stem reticular core.[8]

All neurons of the Ch1–Ch4 cell groups contain AChE and ChAT in the

perikarya, dendrites, and axons. Approximately 90% of Ch1–Ch4 neurons express the p75 low affinity nerve growth factor receptor (NGFr).[9,10] Nearly all Ch1–Ch4 cholinergic neurons of the human brain also express calbindin D28K.[11] Considerable interspecies differences are present in the cytochemical signature of basal forebrain cholinergic neurons.[11] For example, 20–30% of cholinergic neurons in the basal forebrain of the rat contain reduced nicotinamide-adenine-dinucleotide-phosphate-diaphorase (NADPHd) activity (which is now known to overlap with nitric oxide synthase activity[12]), whereas none of the basal forebrain cholinergic neurons in the monkey or human brain do so. Furthermore, the basal forebrain cholinergic neurons of the rat do not express calbindin D28K, whereas almost all Ch1–Ch4 neurons of the monkey and human do. Differences exist among primates as well. For example,

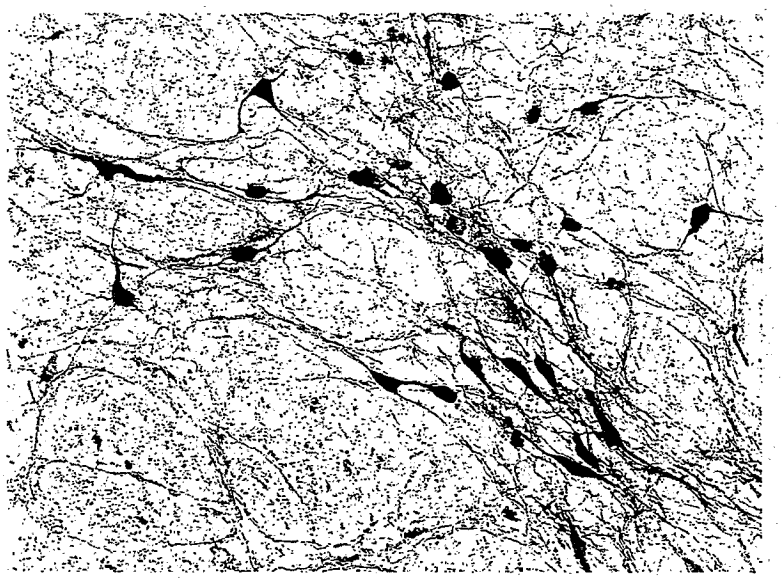

FIGURE 1. Choline acetyltransferase immunocytochemistry in the human brain shows interstitial cholinergic neurons of Ch4 embedded within the internal capsule. Dorsal is to the top and medial to the left. (Magnification, 150×; reduced to 75%.)

Ch1–Ch4 neurons of the monkey express galanin whereas this does not occur in the human brain.[13] Such cytochemical differences need to be taken into account when developing animal models for human diseases that affect the basal forebrain cholinergic cell groups.

Experimental neuroanatomical methods in the monkey brain have shown that different cortical areas receive their major cholinergic input from individual sectors of the NB-Ch4 complex. Thus, Ch4am provides the major source of cholinergic input to medial cortical areas including the cingulate gyrus; Ch4al to frontoparietal and opercular regions and the amygdaloid nuclei; Ch4id-Ch4iv to laterodorsal frontoparietal, peristriate, and midtemporal regions; and Ch4p to the superior temporal and temporopolar areas.[4] The experimental methods that are needed to reveal this

topographical arrangement cannot be used in the human brain. However, indirect evidence for the existence of a similar topographical arrangement can be gathered from patients with Alzheimer's disease. We described two patients in whom extensive loss of cholinergic fibers in temporopolar but not frontal opercular cortex was associated with marked cell loss in the posterior (Ch4p) but not the anterior (Ch4am + Ch4al) sectors of Ch4.[3] This relationship is consistent with the topography of the projections in the monkey brain.

FIGURE 2. Choline acetyltransferase-positive (cholinergic) axons in area 18 of the human brain. Layer I is at the top, layer III at the bottom. The arrow points to a complex preterminal profile. (Magnification, 266×; reduced to 85%.)

The distribution of cholinergic innervation in the human cerebral cortex has been studied in detail with the help of AChE histochemistry, ChAT immunocytochemistry, and NGFr immunocytochemistry.[14–16] All cytoarchitectonic regions and layers of the cerebral cortex display a dense cholinergic innervation (FIG. 2). These fibers have numerous varicosities and, on occasion, complex preterminal profiles arranged in the form of dense clusters. The density of cholinergic axons is higher in the more superficial layers (layers I, II, and the upper parts of layer III) of the cerebral cortex.

Major and statistically significant differences also are found in the overall density of cholinergic axons among the various cytoarchitectonic areas. The cholinergic innervation of primary sensory, unimodal, and heteromodal association areas is significantly lighter than that of paralimbic and limbic areas. Within unimodal association areas, the density of cholinergic axons and varicosities is lower in the upstream (parasensory) sectors than in the downstream sectors. Within paralimbic regions, the nonisocortical sectors have a higher density of cholinergic innervation than the isocortical sectors. The highest density of cholinergic axons occurs in core limbic structures such as the hippocampus and the amygdala.

Within the hippocampal complex, the highest density of AChE-rich cholinergic fibers is seen in a thin band along the inner edge of the molecular layer of the dentate gyrus and within parts of the CA2, CA3, and CA4 sectors. The subiculum has a cholinergic innervation that is lighter than that of the other hippocampal sectors.[17] In the amygdala, each nucleus has a slightly different profile of cholinergic innervation.[18] The density is highest in the central and basal lateral nuclei and lightest in the lateral nucleus. The medial nucleus is the only region of the amygdala that has virtually no cholinergic innervation.

In all cortical and hippocampal fields, NGFr axonal staining is of approximately equivalent density to that of axonal ChAT, providing further evidence that the majority of cholinergic innervation to these regions arises from the Ch1–Ch4 cell groups.[19] The one exception occurs in the amygdala, especially in the basolateral nucleus, which contains very light NGFr staining, raising the possibility that the cholinergic innervation to this nucleus and perhaps to other parts of the amygdala arises from NGFr-negative Ch1–Ch4 neurons or from cholinergic neurons in the brain stem.

POSTSYNAPTIC COMPONENTS OF CORTICAL CHOLINERGIC PATHWAYS

Electronmicroscopic studies in rodents indicate that most cortical cholinergic axons are unmyelinated and that they make symmetrical and asymmetrical synaptic contacts with large numbers of cortical neurons.[20,21] It is also thought that some acetylcholine may be released outside of traditional synaptic contacts and that it may exert its effect by diffusion into receptor-containing sites.[22]

The acetylcholine released from presynaptic cholinergic axons of the cerebral cortex exert their neurotransmitter effects through the mediation of nicotinic and muscarinic receptors. Muscarinic receptors predominate in the mammalian cerebral cortex. Five subtypes of muscarinic cholinergic receptors (m1–m5) have been recognized, each the product of a different gene.[23,24] Three muscarinic receptor subtypes have been characterized pharmacologically (M1–M3), and of these the M1 and M2 subtypes have received the greatest attention. Autoradiographic experiments in the rhesus monkey showed that the pirenzepine-sensitive M1 receptors were far more numerous than M2 receptors. The M1 receptor density reaches the highest levels in components of limbic and association cortex. In contrast, the M2 receptors reach their highest densities in primary sensory and motor areas of the cortex.[25]

Immunocytochemical studies in the human brain have identified cortical neurons which express nicotinic and muscarinic receptors. Such neurons are localized predominantly in the pyramidal neurons of layers III and V. Approximately 30% of immunopositive pyramidal neurons were found to display immunoreactivity for both muscarinic and nicotinic receptors.[26]

It is thought that all cholinoceptive neurons express AChE in order to hydrolyze acetylcholine. However, only a subset of cholinoceptive neurons give an AChE-rich

histochemical reaction.[27,28] Some of these AChE-rich neurons are polymorphic in shape and are distributed preferentially in the deeper cortical layers and the subjacent white matter. Others are pyramidal in shape and are located in layers III and V. Cholinergic axons are thought to express presynaptic autoreceptors which may be involved in the autoregulation of acetylcholine release.

PHYSIOLOGICAL AND BEHAVIORAL IMPLICATIONS

The physiological effect of acetylcholine on cholinoceptive cortical neurons is exceedingly complex. The major effect of acetylcholine is to cause a relatively prolonged reduction of potassium conductance so as to make cortical cholinoceptive neurons more susceptible to other excitatory inputs.[29,30] However, the effect of acetylcholine on cortical neurons can also be inhibitory, either directly or through the mediation of GABAergic interneurons.

Because all regions of the cerebral cortex receive intense cholinergic innervation, it is not surprising that all aspects of cortical function are influenced by cholinergic neurotransmission. In primary visual cortex, for example, cholinergic stimulation does not alter the orientation specificity of a given neuron but increases the likelihood that the neuron will fire in response to its preferred stimulus.[26] An analogous effect has been described in somatosensory cortex.[31]

The Ch1–Ch4 cell groups of the basal forebrain can be considered as a telencephalic extension of the brain-stem reticular formation and also as a direct extension of basomedial limbic cortex. This dual identity helps to explain why arousal and memory are the two major behavioral affiliations of the Ch1–Ch4 cell groups. Experiments in rats have shown that the cortical cholinergic projections from the basal forebrain plays a major role in sustaining at least one component of the hippocampal theta rhythm and also the arousal-related low voltage fast activity of the cortical EEG.[32,33] In a number of animal species, lesions of the Ch4 cell group can cause severe impairments of memory that can be reversed by the systemic administration of agonists.[34,35]

Single-unit studies in monkeys have shown that the neurons of the NB (Ch4) are particularly sensitive to stimulus novelty and to the motivational relevance of sensory cues.[36,37] The novelty and behavioral significance of a sensory event can therefore influence the cortical release of acetylcholine which, in turn, modulates the cortical response to the sensory event. Cortical cholinergic pathways are thus in a position to alter the neural impact of sensory experiences according to their behavioral significance. It is easy to see how such a circuitry would have a major influence on cortical arousal. In keeping with this interpretation, the muscarinic blocking agent scopolamine attenuates the cortical P-300 arousal response that is normally elicited by novel or surprising stimuli.[38]

The relationship of the Ch1–Ch4 cell groups and of cortical cholinergic innervation to memory function is quite complex. Limbic and paralimbic regions of the cerebral cortex are known to play a critical role in memory and learning. The preferential concentration of cholinergic innervation in these parts of cortex may explain why cholinergic antagonists and cholinoactive drugs seem to have a preferential effect on memory, learning, and other limbic functions such as mood, motivation, and aggression.[39–41] The role of acetylcholine in hippocampal long-term potentiation[42] may provide another mechanism that underlies the relationship of cholinergic pathways to memory.

Recent brain slice experiments in piriform cortex of the rat have shown that acetylcholine can selectively suppress intrinsic synaptic transmission through a

presynaptic mechanism, while leaving extrinsic afferent input unaffected. This selective suppression could prevent interference from previously stored patterns during the learning of new patterns. Hasselmo and colleagues[43] argued that this could provide a novel mechanism through which cortical cholinergic innervation could participate in new learning. Buzsaki[44] proposed a model according to which the cholinergic innervation, especially of the hippocampal complex, plays a major role in switching from on-line attentive processing, characterized by the hippocampal theta rhythm, to an off-line period of consolidation, characterized by sharp wave activity (see ref. 45 for review).

Another mechanism that links cholinergic axons to memory and learning may be related to the differential regional density of cortical cholinergic innervation. Experimental evidence leads to the conclusion that sensory-limbic pathways play pivotal roles in a wide range of behaviors related to emotion, motivation, and especially memory.[46,47] The process starts within the primary sensory areas of the cerebral cortex which provide a portal for the entry of sensory information into cortical circuitry. These primary areas project predominantly to upstream (parasensory) unimodal sensory association areas, which, in turn, project to downstream unimodal areas and heteromodal cortex. The heteromodal and downstream unimodal areas collectively provide the major source of sensory information into paralimbic and limbic areas of the brain. Our observations show that the density of cholinergic innervation is lower within unimodal and heteromodal association areas than in paralimbic areas of the brain. In the unimodal areas, moreover, the downstream sectors have a higher density of cholinergic innervation than the upstream sectors. Core limbic areas such as the amygdala and hippocampus contain the highest densities of cholinergic innervation. This pattern of differential distribution led us to suggest that sensory information is likely to come under progressively greater cholinergic influence as it is conveyed along the multisynaptic pathways leading to the limbic system. As a consequence of this arrangement, cortical cholinergic innervation may help to channel (or gate) sensory information into and out of the limbic system in a way that is sensitive to the behavioral relevance of the associated experience. The memory disturbances that arise after damage to the Ch1–Ch4 cell groups or after the systemic administration of cholinergic antagonists may therefore reflect a disruption of sensory-limbic interactions which are crucial for effective memory and learning.

TOWARDS AN EXPANDED ASCENDING RETICULAR ACTIVATING SYSTEM

In addition to Ch1–Ch4, two cholinergic cell groups in the upper brain stem, the Ch5 neurons of the pedunculopontine nucleus and the Ch6 cell group of the laterodorsal tegmental nucleus, are also intimately involved in the modulation of arousal. The Ch5 and Ch6 cell groups provide the major cholinergic innervation of the thalamus. Moruzzi and Magoun[48] had introduced the concept of a brain-stem ascending reticular activating system (ARAS) that acted to desynchronize the cortical electroencephalogram via a relay in the thalamus. Subsequent work revealed that a most important component in this system consists of a cholinergic reticulothalamic pathway that facilitates the activation of corticopetal relay neurons in the thalamus.[49–53]

The physiological relevance of this pathway to the reticular activating system was demonstrated by Kayama and colleagues.[54] They identified the Ch5–Ch6 neurons with NDPHd histochemistry and showed that electrical stimulation of these neurons

causes a scopolamine-sensitive activation of lateral geniculate neurons and even an occasional enhancement of their response to photic stimulation. Electrical stimulation of Ch5 also causes a hyperpolarization of GABAergic neurons in the reticular nucleus of the thalamus. Because the neurons of the reticular nucleus have an inhibitory effect on thalamic relay neurons, the net effect of Ch5 stimulation is to disinhibit thalamic relay nuclei.[30] Thus, the Ch5–Ch6 neurons can facilitate the transthalamic (and ultimately corticopetal) processing of sensory information in ways that could further modulate arousal and attention.

These observations show that the original concept of the ARAS needs to be expanded to include at least two sources of ascending cholinergic projections, a traditional one in the upper brain stem (Ch5–Ch6) and a second one in the basal forebrain (Ch1–Ch4). Noncholinergic regulatory pathways that arise from the hypothalamus (histaminergic), ventral tegmental area (dopaminergic), nucleus locus coeruleus (noradrenergic), and brain-stem raphe (serotonergic) and that send widespread projections to the cerebral cortex and thalamus are also part of this expanded ARAS (see ref. 55 for review). Each of these cholinergic and noncholinergic projections can exert a powerful influence on the information processing state of the thalamus and cerebral cortex in ways that influence attentional, emotional, motivational, and arousal states. The collective activity of these ascending regulatory pathways provides the physiological matrix (or state) within which the discrete, point-to-point projections that interconnect cortex, thalamus, and the basal ganglia can set the vectors of complex behaviors related to cognition and comportment. The rapidly accumulating information on the ascending cholinergic projections provides a blueprint for investigating the characteristics of the other components of this extremely important neural system in the human brain.

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